A copy of the claims showing the changes to the specification and claims is attached as "MARKED-UP VERSION SHOWING CHANGES MADE TO SPECIFICATION AND CLAIMS"

II. REMARKS

Claims 1 and 56 to 89 are pending in the subject application and stand variously rejected by the Office in the outstanding Office Action. By this Amendment and Response, claim 1 has been cancelled without prejudice or disclaimer and claims 56 to 59, 61, 62, 64, 65, 67 to 70 and 86 to 88 have been amended.

These amendments are made without prejudice or disclaimer and are not intended to be a dedication to the public the subject matter of the claims or their equivalents, as filed or preliminarily amended. Applicants reserve the right to pursue the claims as originally filed and preliminarily amended in a later filed continuation application.

The specification has been amended to identify the sequences appearing in the Sequence Listing, as required by the Office and Rules. No new matter has been added.

Support for the amendments to the claims can be found in the specification as originally filed. An issue of new matter is not raised by these amendments and entry thereof is respectfully requested.

In view of the preceding amendments and remarks that follow, reconsideration and withdrawal of the objections to the specification and the rejections of the claims are respectfully requested.

Amended claims 56 to 89 are currently under examination.

Requirement for Sequence Listing in Compliance with 37 C.F.R. §§ 1.821 – 1.825

The Response to the Notice to Comply, Sequence Listing and Diskette as required by the Office was filed with Box Sequence Listing on May 31, 2002. Applicants' undersigned attorney hereby states that the paper copy of the Sequence Listing enclosed with the copy of this Amendment and Response is identical to the electronic copy of same submitted to Box Sequence Listing. In view of the enclosed, reconsideration and withdrawal of the objection is respectfully requested.

Supplemental Information Disclosure Statement

PTO-Forms and a Supplemental Information Disclosure Statement is submitted in response to the Examiner's request for PTO-1449 Forms which list references not already of record and that specify the instant case serial number. Reconsideration and withdrawal of this objection is respectfully requested.

35 U.S.C. § 112, First Paragraph

Claims 1 and 85 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In claims 1 and 85, reference is made to assays using compounds which have been disclosed generically or subgenerically. The Office alleged that this reference to compounds is excessively broad in light of the disclosure wherein only selected compounds have been tested.

Applicant respectfully traverses. By this response, claim 1 has been canceled without prejudice or disclaimer. The cancellation of claim 1 renders the rejection of the claim moot. The rejection of claim 85 is discussed below.

Claims 56-61, 84 and 86-89 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Office alleged that claims 56-61, 81-84 and 86-89 reference is made to methods of treatment using compounds which have been disclosed generically or subgenerically. The Office opined that this reference to compounds is excessively broad in light of the disclosure wherein only selected compounds have been tested and as to the types of cancer which can be treated; no data is provided to show effective treatment of liver cancer.

Claims 62-89 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Office alleged that in claims 62-89 make reference to compounds which have been claimed generically and subgenerically. The Office opined that this reference to compounds is excessively broad in light of the disclosure wherein only selected compounds have been actually synthesized.

Applicants respectfully traverse, with respect to all claims rejected under 35 U.S.C. § 112, first paragraph and on all grounds for rejection.

To satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph, Applicants' specification must teach one of skill in the art how to make and use the invention of the claims without an undue amount of experimentation. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Applicants' specification need not teach and preferably omits what is well known in the art. Hybritech, Inc. v. Monoclonal Antibodies, 802 F.2d 1384, 231 USPQ 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

Applicants' specification sets forth numerous working and prophetic examples that enable the full scope of the claims. See M.P.E.P § 608.01(p)(II) wherein it states that "[s]imulated or predicted test results and prophetical examples (paper examples) are permitted in patent applications."

Absent evidence to the contrary, Applicants' specification must be accepted by the Office as enabling for the full scope of the claims. See In re Marzocchi, 439 F.2d 220, 169 USPQ 369 (CCPA 1971); In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995).

The Office Action does not provide any evidence the above-referenced teachings, in combination with what was known to those skilled in the art, does not enable the full scope of the claims. Removal of the rejections under 35 U.S.C. § 112, first paragraph is respectfully requested.

35 U.S.C. § 112, Second Paragraph

Claims 1 and 56-59, 61-63, 65, 72 and 81-87 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim

the subject matter which Applicants regard as the invention. In claim 57 at line 1, the Office opined that the term "characterized by" is indefinite because the meaning implied by the noted term is not judicially established. The Office also alleged that the term "hyperproliferative cells" is indefinite for failure to specify the particular disease being referred to. The Office further alleged that the term "pathological cell" fails to define the disease in claims 56, 58, 81-84, 86 and 87.

The Office further stated that in claim 58, the terms "a sugar substituent," "a thio sugar substituent,", a carbasugar substituent," and "a seco-sugar sustituent" are allegedly indefinite because they fail to detail structure.

The Office also argued that in claim 59, the term "masked phosphoryl moiety and a phosphoramidatyl moiety" needs the underlined term added (Markush group otherwise incomplete).

The Office further requested that in claim 61, beginning at lines 3, the terms "alkene" and "alkyne" be renamed to -- alkenyl -- and -- alkynyl. The Office additionally requested at the end of line 4, of claim 61 the particular groups being referred to be clarified.

The Office also stated that in claim 62, at lines 10-11, the term "aromatic hydrocarbyl group" does not consist of "one or more unsaturated hydrocarbyl groups," although this may appear to be the case, and that similarly at lines 11-12 a heteroaromatic group (2-, 3-,or 4-pyridinyl radical?) is not correctly defined as consisting of "one or more unsaturated hydrocarbyl groups," wherein no heteroatoms are provided for.

In claim 62 at line 27, the Office stated that the line needs to have the term -- and -- added at the end to make the Markush group proper.

In claim 62 the Office stated that at lines 41 and 42, the terms " -anomeric" is incomplete. (alpha and beta?) and that in claims 63, 65, 72 and 85, punctuation appears to be missing.

Applicants respectfully traverse. The claims have been amended herein in a sincere effort to address and overcome many of the grounds for rejection of the claims under 35 U.S.C. § 112, second paragraph.

With respect to the objection to the term "sugar" etc., Applicants traverse. Two well known tenets of patent law are 1) that an Applicant can be his own lexicographer and 2) that claims are read in light of the specification. Applicants' undersigned attorney directs the Office

to page 35, lines 9 through 24 that specifically defines and provides examples for the allegedly offending terms that define a standard structure. Moreover, such use is consistent with the recognized use of the term in the art. See, for example, pages 1170 through 1180, of an undergraduate organic chemistry text, ORGANIC CHEMISTRY (1973) Morrison & Boyd, Eds. Allyn and Bacon, Inc., Boston, Mass., USA. Thus, Applicants' definition of the term "sugar group" is consistent with the in the chemistry text. Copies of pages 1170 through 1180 are attached for the Office's convenience.

Applicants further direct the Office's attention to pages 530 through 551 from the professional and post-graduate text CHEMISTRY OF NUCLEOSIDES AND NUCLEOTIDES (1994) Townsend, L. Ed., Plenum Press, NY, NY, USA. (copies attached). This partial index of the text contains the terms sugar moieties, sugar rings and sugar hydrazones. Thus, the term "sugar" is well known to one of skill in the art and denotes to them certain defined structures.

With respect to the Office's ground for rejections that the term "pathological" and "hyperproliferative" are vague and indefinite, a common dictionary definition is "relating to or caused by disease." See page 1001 of THE AMERICAN HERITAGE COLLEGE DICTIONARY (1997) Houghton Mifflin Company, Boston, Mass., USA, copy attached. The same dictionary defines the prefix "hyper" to mean "over, above, beyond" (page 668, copy attached) and "proliferate" to mean "to grow or multiply by rapidly reproducing new tissue, parts, cells, or offspring." See page 1094, copy attached. Thus, consistent with Applicants' use, hyperproliferative would be understood to mean to grow or multiply by rapidly reproducing new tissue, parts, cells or offspring at a rate over and above that which is considered normal. Moreover, a search of the U.S. Patent and Trademark Office's public database of issued patents between the years 1996 and 2002 show that 1,012 issued patents contain this term.

Thus, use of the terms "hyperproliferative", "sugar" and "pathological" are terms well known in the art. Removal of these grounds for rejection is respectfully requested.

With respect to the Office's statement that certain claims are indefinite for lacking "structure." Applicants' attorney responds that "structure" is not *a priori*, required to satisfy the requirements of 35 U.S.C. § 112, second paragraph. See, e.g., the claims of U.S. Patent No. 5,981,507, issued Nov. 9, 1999, wherein chemical terms and functional language adequately described novel pharmaceutical compositions. A copy of U.S. Patent No. 5,981,507 is attached.

In view of the preceding amendments and remarks, reconsideration and withdrawal of the rejections of the claims under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Provisional Double Patenting Rejections

Claims 56-61, 81-84 and 86-89 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 1-12 of copending Application No. 09/130,839. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Claim 62-80 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-39 of copending Application No. 09/235,961. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Claims 56-84 and 86-89 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U. S. Patent No. 6,245,750. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

These are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Claims 1, 56-84 and 86-89 of this application conflict with claims of Application Nos. 09/130,839 and 09/235,961. 37 C.F.R. § 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications.

Applicants respectfully defer responding to the provisional objections until allowable subject matter is indicated in one of the allegedly conflicting applications.

III. CONCLUSION

No additional fee, other than the fee for the one month extension of time, is deemed necessary in connection with the filing of this Amendment and Response. However, if the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 50-1189, referencing billing number 19442-7097. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account. Should a telephone advance prosecution of the subject application, the Examiner is invited to contact the undersigned at (650) 849-4950.

DATE: June 3, 2002

Respectfully submitted,

By: Antoinette F. Konski

Antoinette F. Konski
Registration No.: 34,202

McCutchen, Doyle, Brown & Enersen, LLP
Three Embarcadero Center, Suite 1800
San Francisco, California 94111
Telephone: (650) 849-4950
Telefax: (650) 849-4800

Attachments:
1. Supplemental IDS and PTO Form 1449
2. Pages 1170 - 1180, ORGANIC CHEMISTRY (1973) Morrison & Boyd, Eds. Allyn and Bacon, Inc., Boston, Mass., USA.
3. Pages 530 – 551, CHEMISTRY OF NUCLEOSIDES AND NUCLEOTIDES (1994) Townsend, L. Ed., Plenum Press, NY, NY, USA.
4. Page 1001, THE AMERICAN HERITAGE COLLEGE DICTIONARY (1997) Houghton Mifflin Company, Boston, Mass., USA.
5. U.S. Patent No. 5,981,507

MARKED-UP VERSION SHOWING CHANGES MADE

TO SPECIFICATION AND CLAIMS

In the specification:

Page 68, lines 7 to 15 were amended as follows:

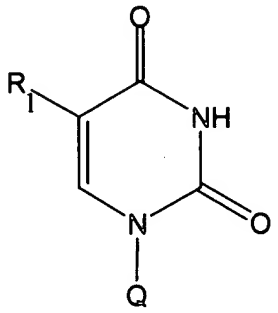
Expression level of human thymidylate synthase transcripts in different cell lines were quantified by using RT-PCR. Oligonucleotide primers for amplification of the human thymidylate synthase and B-actin were designed as follows: Thymidylate synthase sense primer 5'-GGGCAGATCCAACACATCC-3' (SEQ ID No. 1) (corresponding to bases 208-226 of thymidylate synthase cDNA sequence, Genbank Accession No. X02308), antisense primer 5'-GGTCAACTCCCTGTCCTGAA-3' (SEQ ID No. 2) (corresponding to bases 564-583), β-actin sense primer 5'-GCCAACACAGTGCTGTCTG-3' (SEQ ID No. 3) (corresponding to bases 2643-2661 of β-actin gene sequence, Genbank accession no. M10277) and antisense primer 5'-CTCCTGCTTGCTGATCCAC-3' (SEQ ID No. 4) (corresponding to bases 2937-2955).

In the claims:

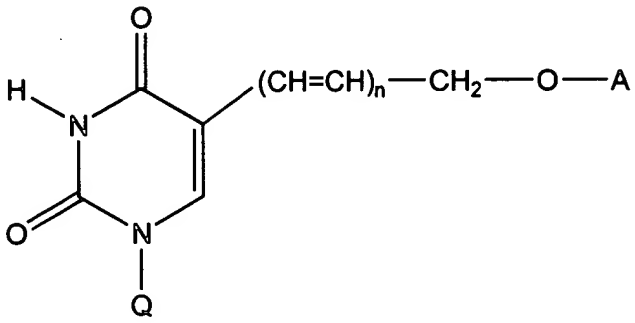
56. (Amended) A method for inhibiting the proliferation of a hyperproliferative cell, comprising contacting the cell with a phosphoryl or [phorphoramidate] phosphoramidatyl prodrug that is selectively converted to a toxin in the cell by an endogenous, intracellular enzyme.

57. (Amended) A method for treating a pathology characterized by hyperproliferative cells in a subject comprising administering to the subject a phosphoryl or [phosphoramidate] phosphoramidatyl prodrug that is converted to a toxin in a hyperproliferative cell by an intracellular enzyme that is endogenously overexpressed or over-accumulated in the cell.

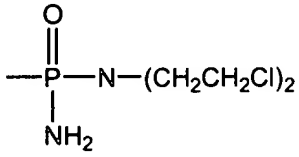
58. (Amended) A method for inhibiting the proliferation of a hyperproliferative cell comprising contacting the cell with an L- or D- isomer of the formula:



wherein R_1 is an electrophilic leaving group; or a compound of the formula:



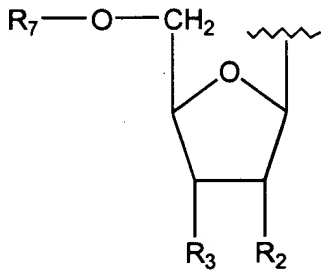
wherein n is an integer from 1 to 10; wherein A is a phosphoryl or [phosphoramidyl] phosphoramidatyl [moiety], or a [substituent] compound of the formula:



wherein Q is selected from the group consisting of a 5' substituted masked phosphoryl, a phosphoryl or [phosphoramidyl] phosphoramidatyl moiety selected from the group consisting of [a sugar groups, thio-sugar groups, carocyclic groups and derivatives thereof] sugar; thio-sugar;

carbocyclic; acyclic analogs and derivatives of a sugar, a thio-sugar or a carbocyclic; derivatives, analogs and pharmaceutically acceptable salts thereof.

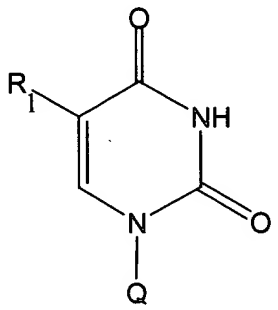
59. (Amended) The method of claim 58, wherein Q has the formula:



wherein R_7 is selected from the group consisting of masked phosphoryl moiety, phosphoramidatyl [phosphoramidyl] moiety, and wherein R_2 and R_3 are the same or different and are independently -H or -OH.

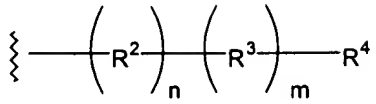
61. (Amended) The method of claim 58, wherein R_1 is [an alkenyl group] of the formula $(-CH=CH)_n-R_4$, wherein n is an integer from 1 to 10, and R_4 is [a substituent] selected from the group consisting of H, a halogen, alkyl, [alkene, alkyne, hydroxy,] alkenyl, alkynyl, hydroxyl -O-alkyl, -O-aryl, O-heteroaryl, -S-alkyl, -S-aryl, -S-heteroaryl, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$, -NHCHO, [a cyanide, cyanate, thiocyanate cyanide, thiocyanate halovinyl substituent, a halomercuric substituent,] -OCN, -SCN, $-N_3$, -NHOH, -NHO-alkyl, and $NHNH_2$.

62. (Amended) A compound of the formula:



wherein:

R^1 is [a substituent] of the formula:



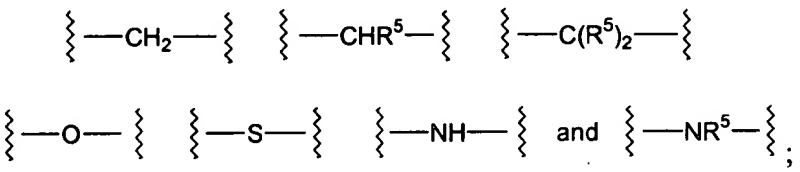
[R^2 is a divalent moiety] wherein n is from 1 to 10 and $\underline{R^2}$ is selected from the group consisting of:

an unsaturated hydrocarbyl group;

an aromatic hydrocarbyl [group consisting of one or more unsaturated hydrocarbyl groups]; and,

a heteroaromatic [group consisting of one or more unsaturated hydrocarbyl groups];

R^3 is selected from the group consisting of:

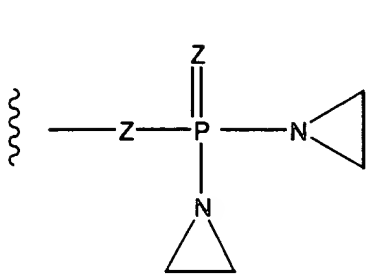


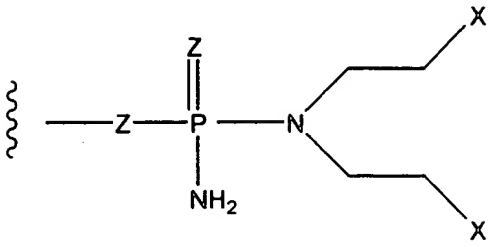
$\underline{\text{wherein}}$ R^5 may be the same or different and is independently a linear or branched alkyl group having from 1 to 10 carbon atoms, or a cycloalkyl group having from 3 to 10 carbon atoms;

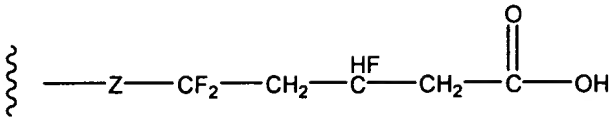
$\underline{\text{wherein}}$ n is an integer from 1 to 10;

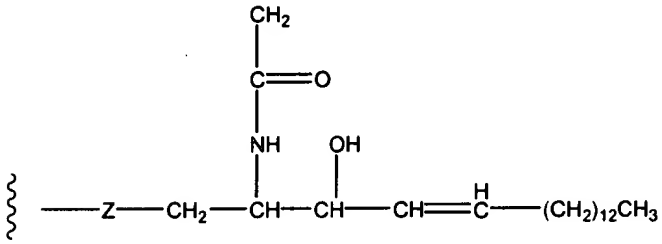
$\underline{\text{wherein}}$ m is 0 or 1;

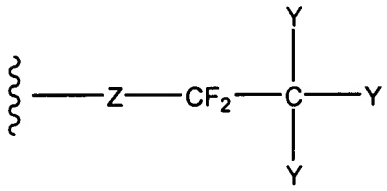
wherein R^4 is a toxophore [moiety] selected from the group consisting of:

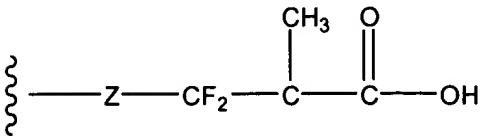


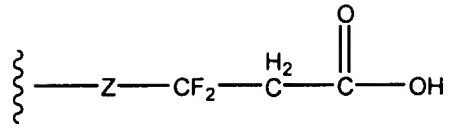




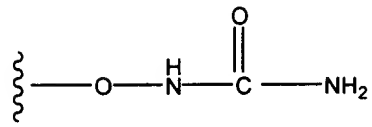








and

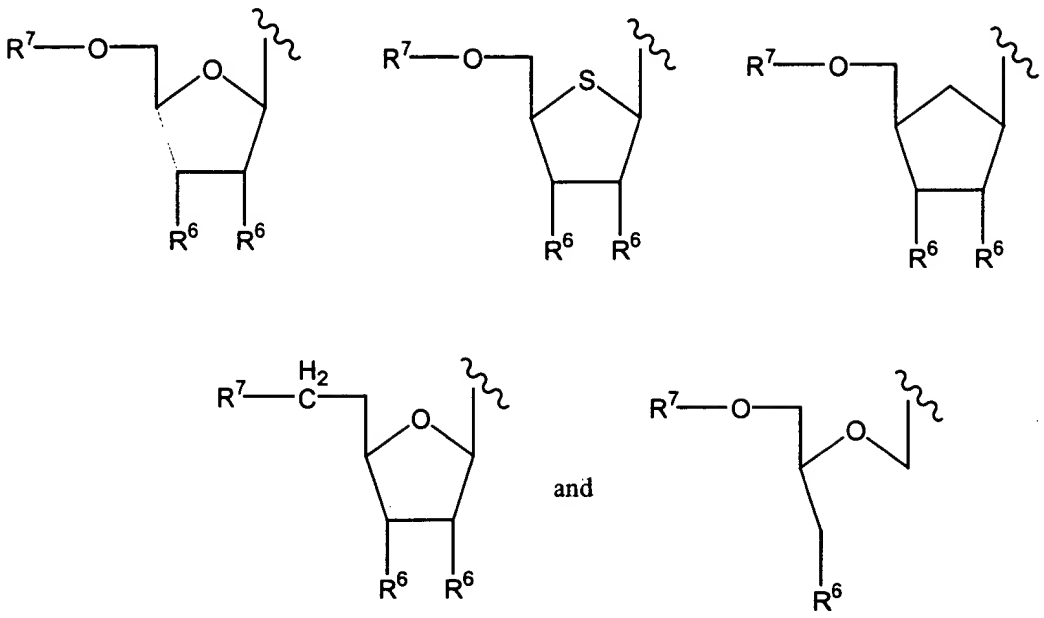


wherein X is -Cl, -Br, -I, or other potent leaving group, with the proviso that when R^7 is -H, and M is zero, then R^4 is not a halogen or when m is zero and n is zero, then R^4 is not a halogen;

wherein Y is independently -H or -F;

wherein Z is independently -O- or -S-;

wherein Q is selected from the group consisting of:



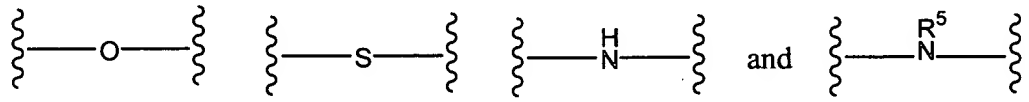
and

wherein R^6 is independently -H, -OH, -OC(=O)CH_3, or -O-Rg wherein Rg is a hydroxyl protecting group other than acetyl; and,

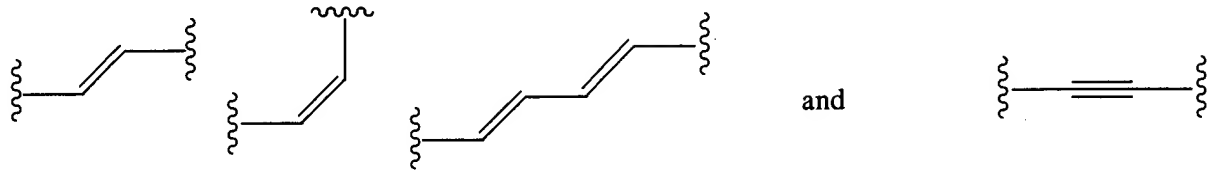
wherein R^7 is hydrogen, a masked phosphate group, or a [phosphoramidate] phosphoramidatyl group;

and wherein said compound may be in any enantiomeric, diasteriomeric, or stereoisomeric form, consisting of a D-form, L-form, α-anomeric form, and β-anomeric form.

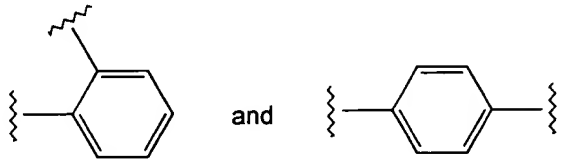
64. (Amended) A compound of claim 62, wherein R^3 is [a divalent spacer moiety] selected from the group consisting of:



65. (Amended) A compound of claim 62, wherein R^2 is [an unsaturated hydrocarbyl group] selected from the group consisting of:

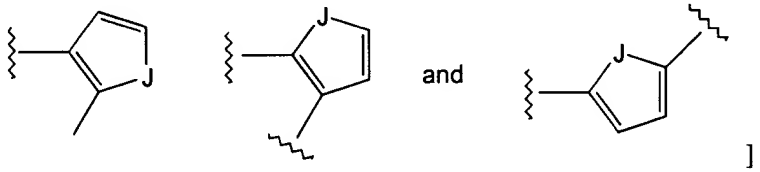


67. (Amended) A compound of claim 62, wherein R^2 is [an aromatic hydrocarbyl group] selected from the group consisting of:

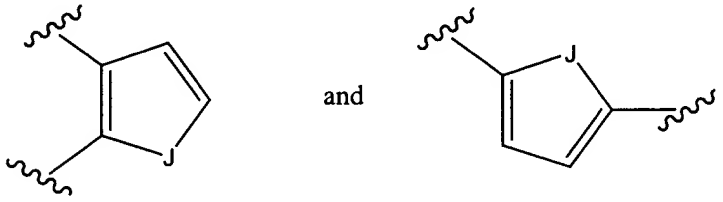


68. (Amended) A compound of claim 62, wherein R^2 is [a heteroaromatic group] selected from the group consisting of:

[



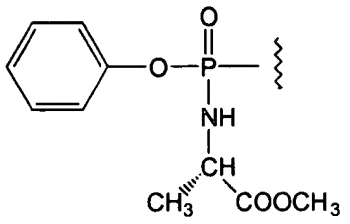
]



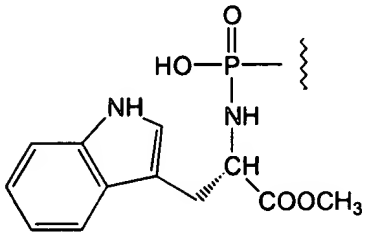
---

wherein J is -O-, -S-, -Se-, -NH-, or $-NR^{ALK}-$, wherein R^{ALK} is a linear or branched alkyl having 1 to 10 carbon atoms or a cycloalkyl group having 3 to 10 carbon atoms.

69. (Amended) A compound of claim 62, wherein R^7 is [selected from the group consisting of:]



70. (Amended) A compound of claim 62, wherein R^7 is [selected from the group consisting of:]



86. (Amended) A method of inhibiting the proliferation of a pathological cell that overexpresses [contains] an intracellular target enzyme, comprising:

(c) contacting the cell with a compound of claim 62; and

(d) allowing the cell to take-up and selectively convert the compound from an inactive state to an active toxic by-product by means of the intracellular target enzyme.

88. (Amended) A method of inhibiting the proliferation of a hyperproliferative cell that overexpresses intracellular [contains] enzymes [that are over expressed] and which contribute to drug resistance, comprising:

(c) contacting the cell with the compound of claim 62; and

(d) allowing the cell to take-up and selectively convert the compound from an inactive state to an active toxic byproduct by means of the enzyme.

88. (Amended) The method of [any of] claims 86 or 87, wherein the hyperproliferative cell is a cancer cell.